Guidance for Industry and FDA Reviewers/Staff

Guidance for Over-the-Counter (OTC) Ovulation Predictor 510(k)s

Document issued on: July 22, 2000

U.S. Department Of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Clinical Chemistry and Clinical Toxicology Branch
Division of Clinical Laboratory Devices
Office of Device Evaluation

Preface

Public Comment

Comments and suggestions may be submitted at any time for Agency consideration to Veronica Calvin, Division of Clinical Laboratory Devices, HFZ-440, 9200 Corporate Blvd, Rockville, MD 20850. Comments may not be acted upon by the Agency until the document is next revised or updated. For questions regarding the use or interpretation of this guidance contact Veronica Calvin at 301-594-1243, extension 151.

Additional Copies

World Wide Web/CDRH home page: http://www.fda.gov/cdrh/ode/guidance/1171.pdf, or CDRH Facts on Demand at 1-800-899-0381 or 301-827-0111, specify number 1171 when prompted for the document shelf number.

Guidance[1] for Over-the-Counter (OTC) Ovulation Predictor 510(k)s

This document presents current approaches and concerns regarding ovulation prediction devices. It is based on 1) current science; 2) clinical experience; 3) previous submissions by manufacturers to the Food and Drug Administration (FDA); 4) the FDA Modernization Act of 1997 (FDAMA); and 5) FDA regulations in the Code of Federal Regulations (CFR). As advances are made in science and technology, and as changes in implementation of legislation occur, these Review Criteria will be re-evaluated and revised as appropriate.

So that the draft may be revised as necessary, please send comments as instructed in the Preface.

DEFINITION: This generic type device is intended for over-the-counter (OTC) use as an in vitro diagnostic (IVD) test for qualitative measurement of luteinizing hormone (LH) in urine. This device is to be used as an aid in ovulation prediction.

PRODUCT CODE: CEP

PANEL: Clinical Chemistry (75)

REGULATION NUMBER: 21 CFR §862.1485

> (a) Identification. A luteinizing hormone test system is a device intended to measure luteinizing hormone in serum and urine. Luteinizing hormone measurements are used in the diagnosis and treatment of gonadal dysfunction.
>
> (b) Classification. Class I (Reserved)

REVIEW REOUIRED: 510(k)

Refer to 21 CFR §807.87 for information provided in a 510(k).

PURPOSE: The purpose of this document is to provide guidance on information to present to the Food and Drug Administration (FDA) before a device may be cleared for marketing. This information enables FDA to make better informed decisions based on a uniform database. It is hoped that such documents may lead to more reliable, reproducible and standardized commercial tests.

[1] This document is intended to provide guidance. It represents the Agency's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

I. Background

Luteinizing hormone (LH) is a glycoprotein produced by the anterior pituitary. It has a molecular weight of 26,000 daltons and is composed of two polypeptide subunits: the alpha-subunit, which is common to LH, follicle stimulating hormone (FSH), human chorionic gonadotropin (hCG), and thyroid stimulating hormone (TSH); and the beta subunit, which confers biological specificity.

LH plays an important role by influencing different functions of both the male and female internal sex organs. In women, LH acts in the final stages of follicular growth to bring about ovulation (or release of the ovum from the follicle) and later maintains the secretory function of the corpus luteum, inducing progesterone production. In men, LH is called interstitial cell-stimulating hormone (ICSH) and acts primarily by stimulating the interstitial Leydig cells in the testes to secrete testosterone.

Levels of LH vary with age and sex and particularly, with the phase of the menstrual cycle. LH increases just before a woman's most fertile day of the month, and this "surge" in LH brings about ovulation within 24 to 36 hours. Increased LH levels are also associated with primary gonadal dysfunction, polycystic ovary syndrome, postmenopause, and pituitary adenoma. Decreased levels of LH are associated with pituitary or hypothalamic impairment, isolated gonadotropic deficiency associated with anosmia or hyposmia, anorexia nervosa, isolated LH deficiency, severe stress, malnutrition, and severe illness.

Such diagnoses usually require use of radioimmunoassay procedures utilizing serum. To determine the preovulatory LH surge and to assess LH secretion throughout the day, immunoassay procedures utilizing urine have primarily been used. Today consumers are able to detect the surge in LH and predict ovulation in the privacy of their homes.

II. Description

These devices primarily consist of a reagent strip in plastic housing. The strip may consist of monoclonal and/or polyclonal antibodies to selectively detect LH in urine. These devices utilize immunochromatographic techniques and incorporate a control mechanism to validate the performance.

III. Performance Characteristics/Laboratory Evaluation

A. Comparison Studies

1. Study Design

Data from at least 100 volunteers are usually evaluated. The home users should collect the samples and perform the tests as outlined in the package insert, without assistance from the professionals.

In addition to comparing the new device to a predicate device (which may be for professional or OTC use), a comparison of the home users' results to the professional users' results on the proposed device is performed. It is recommended that the professional actually perform testing with the consumer's urine on the proposed device. Such testing will simultaneously validate the technical performance characteristics of the device and its labeling based on user experience. Having the professional independently re-read and record their interpretation of the result obtained by the consumer is acceptable as well.

For devices utilizing more than one testing procedure, e.g., urine stream and dip procedure, data should be provided to validate the equivalency of both procedures. This could be achieved by either having half the consumers perform one procedure and half perform the other or having all consumers perform the same procedure and provide data from in-house studies to validate the adequacy of the other procedure. If the latter option is chosen, the consumers should perform the more difficult procedure, i.e., urine stream.

Home users should be randomly selected and should represent diversity of age, background, and education. At the end of testing, users should complete a questionnaire. The questionnaire is to generate feedback on the test, on the ease of use, and clarity and readability of the package insert. A summary of the responses to the questionnaires should be provided in the 510(k) submission.

A summary of the OTC study protocol is helpful in evaluating data and making a substantial equivalence determination.

2. Data Analysis

FDA recommends expressing the data in terms of percent accuracy, which should never exceed >99%. Accuracy, per the NCCLS labeling guideline, is based on test efficiency, i.e., true positive plus true negative results divided by the total number of samples tested.

This performance can be described in text or tabular form. In addition, misleading statements such as: virtually 100% accurate, nearly 100% accurate, 100% accurate, etc., should be avoided.

B. Specificity

The immunological specificity should be determined from cross-reaction with high physiological concentrations of follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), and human chorionic gonadotropin (hCG).

C. Interfering Substances

Interference studies should take into consideration various common chemical, biological, and microbial substances that may be found in urine. These studies can be performed by testing with commonly used prescription and OTC drugs, ascorbic acid, caffeine, glucose, protein, bilirubin, and hemoglobin. Elevated levels of these substances should be spiked into negative and positive urines. Note: The positive urine should have a concentration equivalent to the sensitivity. It is also useful to evaluate varying urine pH levels for potential interference.

D. Sensitivity/Detection Limit

Sensitivity should be evaluated by spiking (adding LH to urine) at least 20 urine samples from either normal, nonpregnant females or males with five different concentrations of LH below, at and above the stated sensitivity. For example, 0, 20, 30, 50, and 100 mIU/mL can be used for a kit with a detection limit of 30 mIU/mL. To support the detection limit, 100% of the samples tested at the claimed sensitivity should be positive and should have reacted within the specified time frame. The concentrations tested should be provided in the 510(k) submission.

E. Standardization

The reference material against which the test is standardized, i.e., World Health Organization's 2nd International Reference Preparation (WHO 2nd IRP) of LH or the 2nd International Reference Preparation of human menopausal gonadotropin (IRP-2-hMG) should be stated in the 510(k) submission.

F. Quality Control

If a device incorporates a procedural or design control, the function of the control should be described and included in the package insert. Examples of descriptions are as follows: the control determines if reagents/chemicals are working properly, the control detects adequate amount of sample, and the control determines if the proper procedure was followed.

Include the components of the control/reference in the 510(k). If the control/reference is set to produce a color intensity equivalent to the sensitivity, please note this in the 510(k) submission.

G. Stability Data

The data showing stability of the reagents need not be submitted to the FDA, but should be kept on file by the manufacturer in accordance with Good Manufacturing Practices (GMP).

A summary of data to support the stability of the results (i.e., maximum time after testing in which the results should be read) should be provided in the 510(k) submission.

H. Antibody Information

Information on characterization and purification of the monoclonal antibody(ies) in the device should be included in the 510(k) submission. If these procedures are performed by another manufacturer, a copy of the Certificate of Analysis from that particular manufacturer should be included in the 510(k) submission.

IV. Labeling

The package insert should be concise, easy to understand, contain illustrations and drawings, and use bold print or other methods to highlight warnings and precautions. The labeling format should conform to the labeling regulations in 21 CFR Part 801, Subpart C and 21 CFR Part 809, Subpart B, Section 809.10. Also, referring to the NCCLS labeling guideline GP14-P (1), DCLD's Points to Consider for Home Use IVDs (2), and CDRH's Write It Right guidance (3) is helpful.

Additionally, FDA has specific recommendations for OTC package inserts. A "Question and Answer"section is usually included. It should contain information related to the test, interpretation of results, interfering substances, accuracy/reliability, and troubleshooting. We recommend that you include a toll-free number or an address in case questions arise concerning the use of the device. We also recommend that information on how the test works be stated near the beginning of the package insert. Also, state in the insert the maximum time after testing in which the results should be read.

Use the outline below for completeness. At a minimum, the package insert should contain the following information:

1. The proprietary name and established name
2. How the test works
3. Warnings and precautions
4. Recommendations for storage
5. Collection of sample and recommendations for sample storage, if applicable
6. Test procedure
7. Interpretation of results (positive, negative, and invalid), including what the control line measures and stability of test reaction

8. Limitations

9. Questions and answers

10. Name and place of business

11. Toll-free number or address

12. Date of issuance/last revision

Examples of limitations that can be included in the insert are listed below. Note: Specific claims should be validated by studies and/or scientific literature.

1. This test is not to be used for contraception (birth control) or as an aid to contraception.

2. Falsely elevated LH may occur in untreated hypothyroid patients due to high levels of thyroid stimulating hormone (TSH).

3. Some other medical conditions such as, pregnancy, postpartum, post abortion, or ovarian cysts may give an inaccurate result.

4. Some prescription drugs (e.g., Pergonal, Danocrine) may affect the result obtained with this test.

5. If you are undergoing therapy with Clomiphene citrate (e.g., Clomid, Serophene), please consult with your physician about how this may affect your result.

6. Medications containing hCG or LH may affect the test and should not be taken while using this test.

7. Most commonly used drugs (e.g., pain relievers, antibiotics) do not affect the test results. (Studies should be performed to validate this claim.)

8. The results of the test may not be valid if you are taking oral contraceptives.

9. A false negative result (i.e., negative when result should actually be positive) can occur with dilute urine samples. It is recommended to reduce water intake 2 hours before testing.

10. Some women do not ovulate every cycle. The LH surge will not be detected in such a cycle.

11. The directions should be followed precisely to get accurate results.

12. Do not use this kit after the expiration date.

13. This test is not reusable.

14. For in vitro diagnostic use (not for internal use).

V. Bibliography

1. National Committee for Clinical Laboratory Standards. Labeling of Home-Use In Vitro Testing Products. NCCLS Document GP14-P, Vol. 9, No. 8, 1989.

2. Report of the CDRH Home-Use IVD Working Group Assessing the Safety and Effectiveness of Home-Use IVDs: Guidance Regarding Premarket Submissions.

3. Write It Right. Recommendations for Developing User Instruction Manuals for Medical Devices Used in Home Health Care.

ABBREVIATIONS

CDRH	Center for Devices and Radiological Health
DCLD	Division of Clinical Laboratory Devices
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GMP	Good Manufacturing Practice
HCG	Human Chorionic Gonadotropin
HMG	Human Menopausal Gonadotropin
ICSH	Interstitial Cell-Stimulating Hormone
IRP	International Reference Preparation
IVD	In Vitro Diagnostic
LH	Luteinizing Hormone
NCCLS	National Committee for Clinical Laboratory Standards
OTC	Over-the-Counter
QC	Quality Control
TSH	Thyroid Stimulating Hormone
WHO	World Health Organization

Checklist

Instructions: Use this checklist for premarket notifications of ovulation predictors intended for home use. Please check the box next to the items below that are included in the premarket notification.

- ❑ CDRH Premarket Submissions Cover Sheet
- ❑ Indications for Use form (required for originals received 1-1-96 and after)
- ❑ Truthful and Accurate statement verbatim as required by 21 CFR 807.87(j). Additions and deletions are not permitted.
- ❑ 510(k) summary **or** statement as required by 21 CFR 807.92 or 21 CFR 807.93 respectively.
- ❑ Summary of OTC study protocol and results
- ❑ Specificity study data
- ❑ Interfering substances study data
- ❑ Sensitivity study data
- ❑ Standardization information
- ❑ Internal control information
- ❑ Monoclonal antibody information
- ❑ Predicate device labeling